ORIGINAL ARTICLE

Granulosa cell tumor of ovary: A clinicopathological study of four cases with brief review of literature

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ABSTRACT

Introduction: Adult granulosa cell tumor (GCT) is a rare ovarian malignancy having good prognosis in comparison with other epithelial tumors. The study aims to collect data of all granulosa cell tumors diagnosed in ESIC Medical College & PGIMSR, Rajajinagar, Bangalore over the last 3 years and to describe the patient profile, ultrasonographic and various histopathological features. **Materials and Methods:** A total of 4 granulosa cell tumors were diagnosed in ESIC Medical College & PGIMSR, Rajajinagar, Bangalore during the period from June 2010 to June 2013. The patient's age, clinical manifestations, radiological and histopathological findings were evaluated. **Results:** All 4 patients were diagnosed as adult granulosa cell tumor, three of four cases were in premenopausal age group and one case was in perimenopausal age. The clinical manifestations were menorrhagia and abdominal pain. Ultrasonographically, 2 cases of granulosa cell tumors were both solid and cystic and one case each was either solid or cystic. Histologically, variety of patterns like diffuse, trabecular, cords, spindle and clear cells were noted. Both Call-Exner bodies and nuclear grooves were observed in all cases. All four cases showed simple hyperplasia without atypia endometrial findings. Follow up on all patients revealed no evidence of recurrence. **Conclusion:** Granulosa cell tumor of the ovary is a rare ovarian entity. The important prognostic factor is staging of the tumor. Staging and histopathology helps in prediction of survival. Also diligent endometrial pathology has to be sorted to rule out endometrial carcinoma.

Key Words: Endometrial pathology, Granulosa cell tumor, histopathological findings, ovary

INTRODUCTION

Adult granulosa cell tumor (GCT) is a rare ovarian malignancy accounting for 1-2% of all tumors and 95% of germ cell tumors originating from sex cord-stromal cells.[1-3] These have good prognosis in comparison with other epithelial tumors. Juvenile GCT, another clinic-histologic subtype of GCT accounts for 5%, occurring at an early age and have increased risk of recurrence.[3-5] Adult GCT has precise clinical, histological and evolutional profile. They frequently occur in postmenopausal women with peak incidence between 50 to 55 years.[1,2] Endometrial reaction to these ovarian tumors is simple hyperplasia while few cases of associated endometrial carcinoma have been reported.[1,2] The present study was undertaken to evaluate epidemiological, various pathological characteristics of GCT and to study associated endometrial changes.

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CASE REPORTS

Case 1

A 37-year female presented to the gynaecology outpatient block with history of menorrhagia. On examination the patient was pale looking and her hemoglobin levels were 8 gm%. Other vitals were stable. Ultrasonogram (USG) revealed left adnexal solid-cystic mass with mild heterogeneity and diagnosis of ovarian tumor was offered. After preoperative investigation the patient was subjected to total abdominal hysterectomy with bilateral

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salphingo-opharectomy (TAH with BSO). On receipt of the specimen, uterus, cervix was unremarkable with the left ovarian encapsulated mass measuring 12 × 9 × 7 cm and stretched out tube over it. Cut section of the lesion showed solid grey white to yellow tumor with tiny multiple cysts, few of which were filled with blood. No normal ovarian stroma was made out. Other adnexae were unremarkable. On histopathological examination (HPE), mass revealed tumor cells being arranged in cords, solid sheets, trabecular pattern and at places microfollicular pattern with Call-Exner bodies. Individual tumor cells are round to oval with nuclear grooves and mitotic figures of 2/10 high power field. Final diagnosis of GCT — Stage 1A — (T1a, N0, M0-TNM and Federation International de Gynecologie et d'Obsterique (FIGO)) was given. Endometrium showed simple hyperplasia without atypia. [Figures 1 and 2]

Case 2

A 34-year female homemaker presented to the causality with history of pain in the abdomen. Subsequent laboratory investigations performed were within normal limits. USG scan showed left ovarian cystic mass, possibly ovarian carcinoma. After pre-operative investigations the patient was subjected to TAH with BSO. HPE of ovarian mass revealed GCT with extensive areas of haemorrhage and cystic change- Stage 1A — (T1a, N0, M0) (FIGO). Associated endometrial simple hyperplasia without atypia was seen.

Case 3

A 40-year-old female presented to the causality with excessive bleeding per vaginum. USG revealed ovarian solid mass and a presumptive diagnosis of ovarian carcinoma was offered. After preoperative investigations the patient underwent TAH with BSO. On table the examination of omental, revealed white firm tiny lesion which was biopsied. On HPE the ovary showed encapsulated lesion composed of cells arranged in trabecular pattern and in sheets were seen. Pleomorphic cells with extensive clear and spindle cell change were observed. A differential of endometriod stromal cell sarcoma ovary and GCT were thought off. Immuno-histochemistry (IHC) for inhibin showed diffuse positivity and further sampling of the lesion showed microfollicle pattern and few oval cells with nuclear folds and grooves, mitotic figures of 4/10hpf which confirmed the diagnosis of GCT - Stage 1A — (T1a, N0, M0). Omental biopsy showed only fibrosis and was free of tumor. Associated simple cystic hyperplasia of endometrium and intramural leiomyoma were noted.

Case 4

A case of 45 years female presented to gynecology outpatient block with pain in abdomen and distension. USG showed ovarian solid cystic mass and diagnosis of ovarian malignancy with ascites was made. Routine laboratory investigations were within normal limits. After preoperative investigation TAH with BSO and omental biopsy was performed. Grossly right ovarian mass measured 12 × 8 × 5 cm and cut surface was grey-white with numerous cystic spaces filled with blood. Representative areas were taken for histopathology. HPE showed tumor composed of sheets of cells. Also they were seen in cords, clusters, microfollicles, Call-Exner bodies, spindle and clear cells. Cells exhibiting nuclear grooves and mitotic figures 2/10hpf were noted. Tumor was seen extending and invading the capsule. Omental tissue was free of tumor and ascitic fluid showed positivity for malignant cells. Special investigation for blood inhibin levels was found to be raised. Final diagnosis of GCT with ascitic fluid extension was made- Stage 1C-(T1C,N0, M0-TNM and FIGO). Endomyometrium showed simple hyperplasia without atypia and adenomyosis.

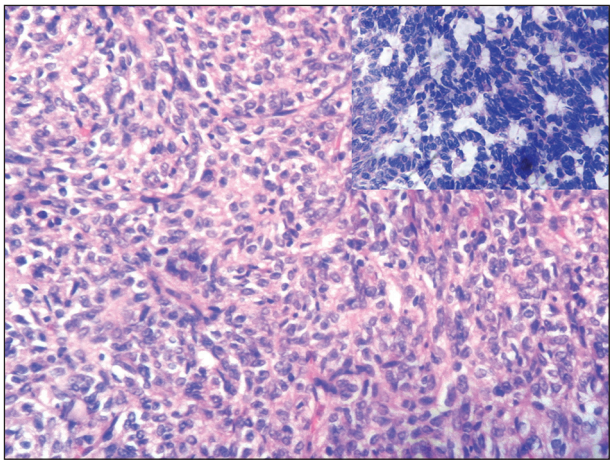

Figure 1: H and E photomicrograph shows Granulosa cell tumour ovary-tumour cells sheets. Inset shows Call-Exner bodies and nuclear grooves (×40)

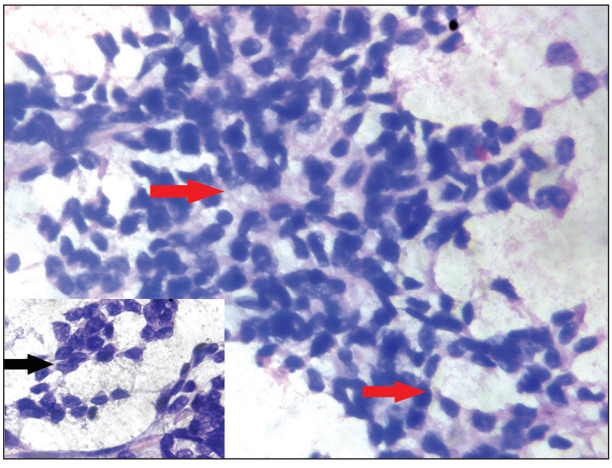

Figure 2: H and E photomicrograph of scrape cytology shows vague Call-Exner bodies (×40). Inset shows nuclear grooves (×100)

DISCUSSION

Granulosa cell tumor of ovary was described by Rokintansky in 1855.[6,7] In our institute over a period of three years, total biopsies were 6969, of which 593 cases were malignant. Of them ovarian malignancies were 10 cases accounting to 1.7%, of which GCTs were 4 cases (0.67%). These are rare malignant tumors with two distinct clinicopathologic subtypes like adult and juvenile. Adult variant is commonest accounting to 95% occurring in peri (40-45 years) and post-menopausal women (>45 years) with peak incidence at 50-55 years.[1,2] Juvenile GCTs are rare neoplasm comprising 5% of all GCTs occurring in the prepubertal age group.[8,9] In the present study three cases presented were in premenopausal and one case in perimenopausal age group [Table 1]. The clinical manifestations ranges from pain abdomen, abdominal distension, menstrual abnormalities like menorrhagia, intermenstrual, postmenopausal bleeding or amenorrhea.[2,3,10] In the present study two of our patients presented with menorrhagia and other two had pain in the abdomen. However, in asymptomatic patients coincidental clinicoradiological examinations plays a role in the diagnosis. Endocrine manifestations are related to estrogen hypersecretion resulting in endometrial hyperplasia, leiomyomas and irregular menstrual abnormalities.[1-3,11] Literature search reveals excessive estrogenic stimulation that leads on to endometrial hyperplasia in 25-50% and subsequent development of endometrial carcinoma in 5-13% of cases.[2,3] Hence, this emphasizes the fact of cautious diligent search of endometrial histology. In the present study all the four patient's endometrial histology revealed simple hyperplasia without atypia and one case each with added adenomyosis and intramural leiomyoma. Radiologically both juvenile and adult GCTs present as large mass measuring upto 12cms in diameter and solid component with multicystic appearance.[2,3,12,13] Similar radiological findings of solid cystic components were seen in two of four cases and one case each with only either solid or cystic component noted in our case series.

The traditional treatment modalities followed are complete surgical excision of tumor with unilateral salphingo-opharectomy in patients desirous of preserving fertility. Total abdominal salphingo-opharectomy with bilateral salphingo-opharectomy in patients with completed family. Occasionally followed up with chemo or radiotherapy.[2,3,14] In all our four cases, surgery was the treatment of choice which included TAH with BSO since all had completed their family. Ultimate final diagnosis is by histopathological analysis. The adult form includes five histologic patterns like micro, macrofollicle, insular, trabecular and spindle/sarcomatoid. Among these microfollicular pattern with Call-Exner bodies and coffee bean nuclei are the commonest diagnostic points.[2,3,15] In the present study all four cases had microfollicular pattern and added two of the cases also showed spindle/sarcomatoid and clear cell subtype. Silver stain shows reticulin fibres around clusters of cells suggestive of GCT. Focal thecal component was seen along with GCT but, however, documented literature necessitates presence of more than 25% of thecal cells to be present to call it a thecoma, which is a benign entity with very good prognosis.[11] The immuno-histochemistry (IHC) markers valuable in this entity are vimentin, CD99 and inhibin.[3] The serum tumor markers raised in GCT are estradiol, inhibin, antimullarian hormone and CA-125.[2,3,16] In the present study only one of our case showed raised inhibin levels done postoperatively. Commonly encountered differential diagnosis for GCT includes endometrioid carcinoma, stromal sarcoma, carcinoid tumors, adenocarcinoma and undifferentiated carcinoma. However histopathology of Call_Exner bodies, nuclear grooves and IHC markers help

Table 1: A profile of patients with adult granulosa cell tumor

Sl no of Case	Age of the pateint	Menopausal status	Clinical presentation	Radiological findings	Histology	Endometrial pathology	Mitotic figures	FIGO staging
Case 1	37 years	premenopausal	menorrhagia	Solid & cystic	Well differentiated-sheets, trabeculae and microfollicles Nuclear grooves	Simple hyperplasia without atypia	2/10 hpf	Stage 1a
Case 2	34	premenopausal	Pain abdomen	Cystic	Well differentiated-sheets, trabeculae and microfollicles Nuclear grooves	Simple hyperplasia without atypia	1/10 hpf	Stage 1a
Case 3	40	premenopausal	menorrhagia		Well differentiated-sheets, trabeculae, microfollicles and spindle cells Nuclear grooves	Simple cystic hyperplasia without atypia and leiomyoma	4/10 hpf	Stage 1a
Case 4	45	perimenopausal	Pain abdomen		Well differentiated-sheets, trabeculae, microfollicles and clear cells Nuclear grooves	Simple hyperplasia without atypia and adeomyosis	2/10 hpf	Stage 1c

in ruling out the differentials.[2,3,17] In the present study, one of our case had differential of endometriod stromal sarcoma and IHC enabled a prompt diagnosis.

Ascitic fluid cytology positive for malignant cells were found in few cases in some of the studies, however survival rate or prognosis for them could not be established.[14] In the present series one of our case presented with ascitic fluid positivity for malignant cells. Various prognostic factors in GCT have been reported of which the staging is a traditional paramount variable. Others include intraperitoneal disease, tumor size, patients age, histologic grade of differentiation, mitotic activity and nuclear atypia.[6,14,17,18] In the present study all four cases presented with early first stage (FIGO-Stage 1). Regular follow-up showed no recurrence or metastasis till date and patients are doing well.

Survival rates after 10 years for stage 1,2,3 and 4 are 87.2%, 75%, 20%, 0% respectively.[3,9,14] In the present study, one of our case showed capsular rupture with positive cytology-Stage 1C. After extensive search the authors found no relevant data regarding this feature helping in further prognostication.[6] Only one study by Bjorkholm *et al*.,[19] documented 60% 25-year survival rate in patients with capsular rupture.

Studies have shown that tumor size less than 10cms have better prognosis.[3,6,10] However, Sehouli *et al*.,[14] stated that smaller tumor may be aggressive due to their biological behavior; hence, tumor size is not a valid prognostic factor. Patients less than 40 years of age are supposedly associated with better prognosis, however, various authors differ in their opinion with regards to significance of patients age and survival.[3,6,14] Histologic grade and mitotic figures show an inverse relation with survival rate.[3,6,8,14,18] In the present case series, all cases were well-differentiated tumors with Mitotic figures 2-4/10 high power fields. Since our follow-up was not upto this period, we are unable to comment on survival rates but still younger age group, early stage and well differentiated tumors helped us predict better prognosis. Recent studies have documented other prognostic factors like pliody, S-phase fraction and p53. However, its relevance as prognostic factors is yet to be investigated further.[14,20]

CONCLUSION

Granulosa cell tumor of the ovary is a rare ovarian entity. Paramount prognostic factor is staging of the tumor. Other prognostic factors are tumor histology, mitotic activity and nuclear grade. Hence staging and histopathology helps in prediction of survival. Also diligent endometrial pathology has to be sorted to rule out endometrial carcinoma which helps in its early detection, better management for patient wellbeing.

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